I. AMENDMENTS

IN THE CLAIMS

Please enter the amendment to claim 8, as shown below.

Cancel claims 21 and 22 without prejudice to renewal.

1.-7. (Canceled)

8. (Currently amended) A method for identifying an agent that modulates a biological activity of DNA-PK, comprising:

a) adding an agent to be tested to a sample, the sample comprising DNA-PK and an immunomodulatory nucleic acid molecule, under conditions which favor binding of the immunomodulatory nucleic acid molecule to DNA-PK, thereby forming a test sample, wherein the immunomodulatory nucleic acid molecule is a DNA molecule that, when bound to Ku antigen, activates DNA-PKcs, wherein the immunomodulatory nucleic acid molecule comprises a nucleotide sequence selected from 5'-Purine-Purine-C-G-Pyrimidine-Pyrimidine-3', 5'-Purine-TCG-Pyrimidine-Pyrimidine-3'; 5'-$(TCG)_n$-3', where n is any integer that is 1 or greater, 5'-Purine-Purine-CG-Pyrimidine-Pyrimidine-CG-3', 5'-Purine-TCG-Pyrimidine-Pyrimidine-CG-3', and 5'-Purine-Purine -CG-Pyrimidine-Pyrimidine-CG-3'; and

b) detecting a biological activity of DNA-PK protein in the test sample, as compared to a control sample lacking the agent, wherein an increase or a decrease in the biological activity of DNA-PK indicates that the agent modulates a biological activity of DNA-PK.

9. (Original) The method of claim 8, wherein the biological activity of DNA-PK is binding to an immunomodulatory nucleic acid molecule.

10. (Original) The method according to claim 9, wherein the method is a cell-free method, and the immunomodulatory nucleic acid molecule is detectably labeled.

11. (Original) The method of claim 8, wherein the biological activity of DNA-PK is activation of DNA-PKcs kinase activity.

12. (Original) The method of claim 8, wherein the method is a cell-based method and modulation of DNA-PK activity is detected by measuring an amount of IL-6 or IL-12 produced by the cell.

13.-22. (Canceled)

II. REMARKS

Formal Matters

Claims 8-12 are pending after entry of the amendments set forth herein.

Claims 8-12, 21, and 22 were examined and were rejected.

Claim 8 is amended. The amendment to claim 1 was made solely in the interest of expediting prosecution, and is not to be construed as an acquiescence to any objection or rejection of any claim. Support for the amendment to claim 1 is found in the claims as originally filed, and throughout the specification, in particular at the following location: paragraph 0077 (pages 21-22). Accordingly, no new matter is added by this amendment.

Claims 21 and 22 are canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claims. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Examiner interview

The undersigned Applicants' representative wishes to thank Examiner Chakrabarti for the courtesy of a telephonic interview, which took place on August 27, 2003, and which was attended by Applicants' representative Paula A. Borden and Examiner Chakrabarti. During the interview, the rejections of the pending claims under 35 U.S.C.§103 were discussed. A claim amendment was also discussed. The claim amendments and statements made herein reflect comments made during the telephonic interview.

During the interview, Examiner Chakrabarti requested that Applicants point out support in the specification for the phrase "wherein the immunomodulatory nucleic acid molecule is a DNA molecule that, when bound to Ku antigen, activates DNA-PKcs." Support for this phrase was pointed out in the amendment, filed on May 21, 2003 and responsive to the March 17, 2003 Office Action, wherein Applicants note that support for this phrase is found in the specification at, e.g., paragraph 0029 (page 8). The specification states, in paragraph 0029, that immunomodulatory nucleic acid molecules bind to Ku antigen, resulting in activation of DNA-PKcs.

Rejections under 35 U.S.C.§103(a)

Claims 8-11 and 22 were rejected under 35 U.S.C.§103(a) as allegedly obvious over Dynan (WO 99/33971) in view of Dynan (U.S. Patent No. 6,441,158; "Dynan '158"). Claims 12 and 21 were rejected under 35 U.S.C.§103(a) as allegedly obvious over Dynan (WO 99/33971) in view of Dynan '158 and further in view of WO 99/11275.

Claims 21 and 22 are canceled without prejudice to renewal, thereby rendering rejection of these claims moot.

Comments regarding obviousness

To establish a prima facie case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. *In re Fine*, 5 USPQ2d 1596 (Fed. Cir. 1988); *In re Jones,* 21 USPQ2d 1941 (Fed. Cir. 1992). Second, there must be a reasonable expectation of success. *In re Merck & Co., Inc.*, 231 USPQ 375 (Fed. Cir. 1986). Finally, the prior art reference, or references when combined, must teach or suggest all the claim limitations. *In re Royk*a, 180 USPQ 580 (CCPA 1974). All three criteria must be met. If any one of these three criteria is not met, a *prima facie* case of obviousness has not been established.

Claims 8-11 and 22 over WO 99/33971 in view of Dynan '158

The Office Action stated:

1) WO 99/33971 teaches a method for identifying an agent that modulates a biological activity of DNA-PK, comprising adding an agent to be tested to a sample comprising DNA-PK and an immunomodulatory nucleic acid molecule; and detecting a biological activity of DNA-PK;
2) WO 99/33971 does not teach a method wherein the immunomodulatory nucleic acid is a DNA molecule that, when bound to Ku antigen, activates DNA-PKcs;
3) Dynan '158 teaches a method wherein the immunomodulatory nucleic acid molecule is a DNA molecule that, when bound to Ku antigen, activates DNA-PKcs;
4) WO 99/33971 does not teach a method wherein the immunomodulatory nucleic acid molecule is a DNA molecule comprising 5' CG 3'; and
5) Dynan '158 teaches a method wherein the immunomodulatory nucleic acid molecule is

a DNA molecule comprising the sequence 5' CG 3'.

The Office Action stated that it would have been obvious to combine and substitute the method wherein the immunostimulatory nucleic acid molecule is a DNA molecule that, when bound to Ku antigen, activates DNA-PKcs of Dynan '158 in the method of WO 99/33971. Applicants respectfully traverse the rejection.

As a first note, Applicants point out that WO 99/33971 and Dynan '158 **are essentially the same reference**. The disclosure relied upon in the Office Action in rejecting the claims is the same in both WO 99/33971 and Dynan '158. Dynan '158 and WO 99/33971 both claim priority to 60/070,278. Dynan '158 and WO 99/33971 both discuss the fact that Ku antigen binds to double-stranded DNA ends, and that in the presence of DNA ends, Ku protein can interact with the catalytic subunit of DNA-PK (DNA-PKcs). Dynan '158 and WO 99/33971 both discuss RNA oligomers in Table 1. Dynan '158 and WO 99/33971 both present Example 4, which describes the observation that the RNA oligomers discussed in these publications **block the ability of Ku protein to activate DNA-PK**. WO 99/33971, page 1; page 7, line 9 to page 8, line 12; Table 1; and Example 4, page 45, line 1 to page 46, line 22. Dynan '158, column 1; columns 5 and 6 and Table 1; and Example 4, column 28.

1. *There is no suggestion or motivation to modify or combine the cited references.*

The Office Action stated that Dynan '158 states that interaction of Ku protein and DNA is involved in the activation of DNA-PK kinase activity. However, Dynan '158 merely discusses what was already known in the art, i.e., that Ku antigen binds to double-stranded DNA ends, and that in the presence of DNA ends, Ku protein can interact with the catalytic subunit of DNA-PK.

There is no motivation or suggestion in the cited references to modify the assay discussed in Example 4 to include an **immunomodulatory nucleic acid molecule**, wherein the immunomodulatory nucleic acid molecule is a **DNA molecule** that, when bound to Ku antigen, **activates DNA-PKcs**. Accordingly, there is no motivation to modify the cited references. Whether there is any motivation to combine the cited references is irrelevant, as the cited references are essentially the same.

2. *There is no reasonable expectation of success in the cited references.*

Both WO 99/33971 and Dynan '158 discuss the use of **RNA oligomer** that **block the ability of Ku protein to activate DNA-PK**. Neither WO 99/33971 nor Dynan '158 discuss a method of identify agents that **activate** DNA-PK using a **DNA molecule**. Neither WO 99/33971 nor Dynan '158 discuss the possibility of using immunomodulatory nucleic acids that are DNA molecules and that, when bound to Ku antigen, activate DNA-PKcs, in a screening assay to identify agents that activate DNA-PK. Accordingly, there is no reasonable expectation of success in the cited references.

3. *The cited references do not teach or suggest all the claim limitations.*

Neither WO 99/33971 nor Dynan '158 teach or suggest a method of identifying an agent that modulates a biological activity of DNA-PK that involves use of an immunomodulatory nucleic acid molecule, wherein the immunomodulatory nucleic acid molecule is a **DNA molecule** that, when bound to Ku antigen, **activates DNA-PKcs**.

The final Office Action stated that the rejection is based on the fact that nucleic acid molecules, capable of binding with Ku protein, can modulate the immune system, because Ku protein was first identified as an autoantigen in sera from certain patients with autoimmune disease, and Ku protein is the regulatory component of the DNA-dependent protein kinase.

However, the presence of Ku antigen in sera of certain patients with autoimmune disease does not in any way lead to a conclusion that nucleic acid molecules capable of binding to Ku antigen modulate the immune system. The Office Action has provided no basis in fact for making such a conclusion. If the Examiner knows of facts that would support such a conclusion, Applicants respectfully request that the Examiner submit an affidavit showing such facts, as provided for under 37 C.F.R.§104(d)(2).

Notwithstanding the above comments, and solely in the interest of expediting prosecution, claim 8 is amended to recite nucleotide sequences. Support for this amendment is found in the specification at, e.g., paragraph 0077 (pages 21-22).

Claims 12 and 21 over WO 99/33971 in view of Dynan '158 and WO 99/11275

The Office Action stated: 1) WO 99/33971 in view of Dynan '158 teaches the method of claims 8-11 and 22; 2) WO 99/33971 in view of Dynan '158 does not teach the method wherein an amount of IL-12 produced by the cell is measured; 3) WO 99/11275 teaches a method wherein an amount of IL-12 produced by a cell is measured; 4) WO 99/33971 in view of Dynan '158 does not teach the method, wherein the immunomodulatory nucleic acid molecule comprises the nucleotide sequence 5'-Purine-Purine-C-G-Pyrimidine-Pyrimidine-3'; and 5) WO 99/11275 teaches a method wherein the immunomodulatory nucleic acid molecule comprises the nucleotide sequence 5'-Purine-Purine-C-G-Pyrimidine-Pyrimidine-3'. The Office Actions stated that it would have been obvious to combine and substitute the method wherein IL-12 is measured, and the immunomodulatory nucleic acid molecule comprises the nucleotide sequence 5'-Purine-Purine-C-G-Pyrimidine-Pyrimidine-3'. Applicants respectfully traverse the rejection.

The reference teachings do not teach or suggest all of the claim limitations. As noted above, neither WO 99/33971 nor Dynan '158 teach or suggest a method of identifying an agent that modulates a biological activity of DNA-PK that involves use of an immunomodulatory nucleic acid molecule, wherein the immunomodulatory nucleic acid molecule is a **DNA molecule** that, when bound to Ku antigen, **activates DNA-PKcs**. WO 99/11275 does not cure the deficiency of WO 99/33971 or Dynan '158. WO 99/11275 discusses detection of IL-12, and discusses immunomodulatory nucleic acid molecule comprising the nucleotide sequence 5'-Purine-Purine-C-G-Pyrimidine-Pyrimidine-3'. However, WO 99/11275 neither discloses nor suggests any immunomodulatory nucleic acids that bind to Ku antigen and activate DNA-PKcs, or any method of identifying agents that modulate DNA-PK activity. Accordingly, neither WO 99/33971 nor Dynan '158, alone or in combination with WO 99/11275, renders instant claims 12 and 21 obvious.

There is no motivation to combine the cited references. As noted above, neither WO 99/33971 nor Dynan '158 disclose immunomodulatory nucleic acids, nor any use of such in an assay to detect agents that modulate DNA-PKcs activity, wherein the immunomodulatory nucleic acid molecule is a **DNA molecule** that, when bound to Ku antigen, **activates DNA-PKcs**. Neither WO 99/33971 nor Dynan '158 even mention an immunomodulatory nucleic acid that, when bound to Ku antigen, activates DNA-PKcs. WO 99/33971 and Dynan '158 only discuss **RNA oligomers** that **block the ability of Ku**

protein to activate DNA-PK. As such, there would have been no motivation to look to WO 99/11275 for immunomodulatory nucleic acids, or assays involving detecting IL-12.

Applicants submit that the rejection of claims 8-12, 21, and 22 under 35 U.S.C. §103(a) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL168.

Respectfully submitted,
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Date: Sept. 15, 2003

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